

Atrazine

10-1-93

RfD-1

## REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Atrazine  
CASRN: 1912-24-9

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts.

RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

## RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 3.5 mg/kg-day [Study 1 NOAEL(adj)]  
UF: 100 MF: 1 RfD: 3.5E-2 mg/kg-day Confidence: High

Crit Effect: (1) Decreased body weight gain  
(2) Cardiac toxicity and moderate-to-severe dilation of the right atrium

	NOAEL (Study 1)	LOAEL (Study 1)
Reported	70 ppm	500 ppm
ADJ	3.5 mg/kg-day	25 mg/kg-day
Study Type	2-Year Rat Feeding Study	2-Year Rat Feeding Study
Reference	Ciba-Geigy Corp., 1986	Ciba-Geigy Corp., 1986

Other Refs: (2) Ciba-Geigy Corp., Agricultural Division, 1987a

1) Ciba-Geigy Corp., 1986  
2-Year Rat Feeding Study

Critical Effect: Decreased body weight gain

## Defined Dose Levels:

NOAEL= 70 ppm  
NOAEL(ADJ)= 3.5 mg/kg-day  
LOAEL= 500 ppm  
LOAEL(ADJ)= 25 mg/kg-day

Conversion Factors: 1 ppm = 0.05 mg/kg-day (assumed rat food consumption)

2) Ciba-Geigy Corp., Agricultural Division, 1987a  
1-Year Dog Feeding Study

Critical Effect: Cardiac toxicity and moderate-to-severe dilation of

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the right atrium

## Defined Dose Levels:

NOAEL= 150 ppm

NOAEL(ADJ)= 4.97 mg/kg-day

LOAEL= 1000 ppm [33.65 mg/kg-day (Male) 33.8 mg/kg-day (Female)]

LOAEL(ADJ)=

Conversion Factors: None

## DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

Ciba-Geigy Corporation. 1986. MRID No. 00141874, 00157875, 00158930, 40629302. HED Doc. No. 005940, 006937. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, Agricultural Division. 1987a. MRID No. 40431301, 41293801. HED Doc. No. 006718, 006937, 007647. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of Sprague-Dawley rats (20/sex/dose for the chronic study, 50/sex/dose for the oncogenicity study) were administered atrazine in the diet for 2 years at dietary concentrations of 0, 10, 70, 500, and 1000 ppm (0, 0.5, 3.5, 25 and 50 mg/kg-day) (Ciba-Geigy Corp., 1986). An additional 10 rats/sex were placed on control and high-dose (1000 ppm) diets for a 12-month interim sacrifice and 10/sex (control and high-dose) for a 13-month sacrifice (the 1000 ppm group was placed on control diet for 1 month prior to sacrifice). Animals were caged individually and received food and water ad libitum.

In males, survival was increased in a dose-related manner ( $p < 0.003$ , using the Cox Tarone test) and was significantly higher in males receiving 1000 ppm when compared with controls ( $p = 0.0055$ , using pairwise comparison). In contrast, survival in females was decreased in a dose-related manner ( $p$  value for a negative trend = 0.0016) and was significantly lower ( $p = 0.0042$ ) in high-dose females when compared with controls.

Mean body weights were significantly depressed ( $p < 0.01$ ) in males and females receiving 500 (M: 8%; F: 19%) and 1000 (M: 19%; F: 27%) ppm with the exception of mean weights for males in the last 2 months of the study. The 24-month weight gain in the high-dose animals was 76% of control for males and 64.5% of control for females. In the recovery groups, the weight gain for month 13 for males previously receiving 1000 ppm was 63 +/- 14.6 g, compared with 20 +/- 17.9 g for controls ( $p < 0.01$ ), and for females previously receiving 1000 ppm it was 56 +/- 31.6 g, compared with 16 +/- 11.9 g for controls ( $p < 0.01$ ). However, the mean weight at 13 months in these males was still significantly ( $p < 0.01$ ) lower than controls.

In females receiving 1000 ppm, statistically significantly ( $p < 0.05$ ) lower mean red cell count, hemoglobin and hematocrit were noted at 6, 12, and 18 months when compared with controls. The values were somewhat depressed in high-dose females at 24 months: however, only four females were used for clinical studies. Red cell count, hemoglobin and hematocrit were also decreased in the 10 females receiving 1000 ppm and scheduled for sacrifice at 12 months. The values approached control levels at 13 months in the 1000 ppm recovery group. All values for parameters in dosed males were similar to those in the control

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groups with the exception of an increased mean platelet count at 6 months in rats receiving 1000 ppm. Increase platelet counts were also seen at 6 and 12 months in females receiving 1000 ppm. The level of serum triglycerides in high-dose males ( $56.55 \pm 18.12$  mg/dL) was, in general, lower than control values ( $139.26 \pm 88.35$  mg/dL) throughout the study; however, the decrease was significant ( $p < 0.05$ ) only at 6 months. In groups scheduled for the 12-month sacrifice, the level in high-dose males ( $103.1 \pm 47.81$  mg/dL) was significantly lower ( $p < 0.01$ ) than in control males ( $228.3 \pm 95.44$  mg/dL). At the 13-month sacrifice, the triglyceride level was similar in control males and those that had previously received 1000 ppm. In females, glucose levels were decreased ( $p < 0.01$ ) in the high-dose group at 3, 6 and 12 months when compared with controls.

The absolute weight of liver and kidney in high-dose males sacrificed at 12 months was significantly ( $p < 0.05$ ) lower than controls. The mean weight of the liver was  $14.71 \pm 2.81$  g for the high-dose groups and  $19.7 \pm 3.46$  g for the controls; the mean weight of the kidneys was  $3.67 \pm 0.4$  g for high-dose males, compared with  $4.39 \pm 0.58$  g for controls.

At 24 months, the mean absolute weights of liver and kidney in high-dose males were lower than those of controls, but the decrease was not statistically significant. There were no other changes in absolute organ weights of males and females. There were several increases in organ-to-body weight ratios in high-dose animals that were significant ( $p < 0.05$ ) when compared with controls but they were not accompanied by changes in absolute organ weights. These changes were the result of decreased body weights.

Acinar hyperplasia of the mammary gland and epithelial hyperplasia of the prostate were increased in males receiving 1000 ppm when compared to controls. In females receiving 500 or 1000 ppm, there was an increased myeloid hyperplasia in the bone marrow of both the femur and sternum. It was reported that the bone marrow changes, as well as an increase in extramedullary hematopoiesis in the spleen, were sequelae related to mammary fibroadenomas and adenocarcinomas. The myeloid hyperplasia was characterized by a decrease in the number of fat cells in the marrow and an increase in the hematopoietic tissue, particularly cells of the granulocytic series. Muscle degeneration (femoral muscle) was found in both high-dose males and females. Retinal degeneration was increased in both males and females, the incidence being significantly ( $p < 0.05$ ) higher in high-dose females than in controls. In high-dose females there was an increase in coagulative centrilobular necrosis in the liver.

Based on decreased body weight gain, the LEL for systemic toxicity is 500 ppm (25 mg/kg-day). The NOEL for systemic toxicity is 70 ppm (3.5 mg/kg-day).

Groups of 5-month-old beagle dogs (6/sex control, 4/sex low- and mid-dose, and 6/sex high-dose) were administered atrazine for 1 year at dietary levels of 0, 15, 150 and 1000 ppm (Male: 0, 0.48, 4.97 and 33.65 mg/kg-day; Female: 0, 0.48, 4.97 and 33.8 mg/kg-day) (Ciba-Geigy Corp., Agricultural Div., 1987a). Animals received food and water ad libitum.

The most significant effect of atrazine administration was the syndrome of cardiopathy, featuring discrete myocardial degeneration, which was most prominently found in animals receiving 1000 ppm. Clinical signs referable to cardiac toxicity, such as ascites, cachexia, labored/shallow breathing, and

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abnormal EKG (irregular heart beat and increased heart rate, decreased P-II values, atrial premature complexes, atrial fibrillation) were first observed as early as 17 weeks into the study. Gross pathological examination revealed moderate-to-severe dilation of the right atrium (and occasionally the left atrium), microscopically manifest as atrophy and myelosis (degeneration of the atrial myocardium).

Three animals had to be sacrificed during the study in moribund condition: one 150 ppm male on day 75; one 1000 ppm female on day 113; and one 1000 ppm male on day 250. Control and 15 ppm animals survived the entire study period without incident. The study authors concluded that only the death of the high-dose female was compound related.


No effects were observed in the low- and mid-dose groups. Therefore, based on the effects observed in the high-dose group, the LEL for systemic toxicity is 1000 ppm (Male: 33.65 mg/kg-day; Female: 33.8 mg/kg-day). The NOEL for systemic toxicity is 150 ppm (4.97 mg/kg-day).

One hundred twenty male and 120 female Charles River CD rats were randomly distributed into four treatment groups, 0, 10, 50 and 500 ppm (Male: 0, 0.69, 3.5 and 34.97 mg/kg-day; Female: 0, 0.76, 3.78 and 37.45 mg/kg-day) (Ciba-Geigy Corp., Agricultural Div., 1987b). Male rats were placed on the control and test diets at 47 days of age and females at 48 days of age. They were maintained on these diets for a period of 10 weeks prior to mating. Males and females were housed together in a 1:1 ratio for mating. One litter was produced in each generation. After weaning of the first generation, 30 males and 30 females were selected for the second parental generation. The remaining male parental animals were sacrificed on days 133-134 of the study. Animals selected for the second generation were exposed to test diets for 12 weeks prior to mating. Mating was conducted in the same manner as for the first generation. Parental males were sacrificed on day 138 of the study and parental females on days 138, 139 and 152 after weaning of their litters.

Body weights were statistically significantly ( $p < 0.05$ ) lower for high-dose animals (14% and 16% for the F0 and F1 males, respectively; 14% and 13% for the F0 and F1 females, respectively) throughout the study. Body weight gains were also statistically significantly depressed ( $p < 0.05$ ) at the high-dose (27% and 17% for the F0 and F1 males, respectively; 28% and 15% for the F0 and F1 females, respectively). At the mid-dose, sporadic decreases in body weight gain were also noted. These changes were not considered to be treatment-related since they were occasional and sporadic. Food consumption was statistically significantly reduced for males and females during the premating period for both parental generations and for F1 females on days 0-7 of gestation. No other effects were noted.

Based on the effects observed at the high-dose, the LEL for parental toxicity is 500 ppm (Male: 34.97 mg/kg-day; Female: 37.45 mg/kg-day). The NOEL for parental toxicity is 50 ppm (Male: 3.5 mg/kg-day; Female: 3.78 mg/kg-day).

In the initial Office of Pesticide Programs (OPP) review of this study for reproductive effects, a NOEL and LEL of 10 and 50 ppm were selected based on a statistically significant ( $p < 0.05$ ) decrease in the F2 generation male pup body weights at day 21. The registrant subsequently submitted the original and revised "Healy analyses" for the F1 and F2 male and female body weights. This method of analysis was proposed by M.J.R. Healy, who observed that "experiments



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using animal litters as experimental units usually require a weighted analysis to allow for variations in litter size" and described "methods for assessing appropriate weights" (Healy, 1972). The registrant contended that a review of the original Healy analysis procedure determined that pairwise comparisons should not have been conducted in the absence of a statistically significant F-statistic. The correct procedure, as the registrant pointed out, is to carry out pairwise comparisons only if the F-Test is significant, thereby controlling the Type I (false-positive) error rate. Therefore, the revised Healy analysis should be considered correct as far as determining which differences are statistically significant. Therefore, the registrant concluded that the NOEL for reproductive toxicity should be greater than 10 ppm.

Upon reviewing this additional information, the OPP toxicologists and statisticians concluded that the NOEL and LEL for reproductive toxicity be changed to 50 and 500 ppm respectively, based on reduced body weight in the F2 generation male pups at lactation days 7 and 14. Further rationale for this change is described below.

Body weights of the F2 male pups in the 10 and 50 ppm groups at day 7 (13.39 g and 13.66 g, respectively) and day 14 (28.26 g and 28.33 g, respectively) are essentially the same even though they are less than the control group value (14.01 g and 29.32 g for days 7 and 14, respectively). The day 4 post-culling data should be used as a control time point to determine the lactational effect endpoint. The added week of additional compound intake, especially at 500 ppm, is expected to further increase the body weight reduction changes already seen.

The only change noted at 500 ppm was a consistent, though not statistically significant, fall in F2 male pup body weights at 500 ppm (9.02, 13.28 and 28.06 g, for days 4, 7 and 14, respectively) when compared to the post culling controls (9.29, 14.01 and 29.32 g for days 4, 7 and 14, respectively). Therefore, the decreases in body weights of the F2 male pups are considered to be an equivocal biological effect.

Based on an equivocal decrease in body weights of the F2 male pups, the LEL for reproductive toxicity is 500 ppm (Male: 34.97 mg/kg-day; Female: 37.45 mg/kg-day). The NOEL for reproductive toxicity is 50 ppm (Male: 3.5 mg/kg-day; Female: 3.78 mg/kg-day).

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UNCERTAINTY AND MODIFYING FACTORS

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## UNCERTAINTY FACTORS:

The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for intraspecies-variability.

## MODIFYING FACTORS:

None

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ADDITIONAL COMMENTS / STUDIES

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In the previous review of atrazine, a core grade supplementary 2-year feeding study in dogs (Ciba-Geigy Corp., 1964) with a systemic NOEL and LEL of 0.35 and 3.54 mg/kg-day, respectively, was included under other data reviewed. Since the stated NOEL for this study was approximately 10-fold lower than the NOEL

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established in a newer 1-year dog study (Ciba-Geigy Corp., 1987a), a reevaluation of the older study by the Office of Pesticide Programs (OPP) was considered necessary. OPP's reevaluation noted the following deficiencies: 1) purity of test material was not reported; 2) only 3/dogs/sex were used, animals were obtained from different suppliers and weights of individual animals were not provided; 3) animals were given double portions of food on Saturdays and none on the following day; 4) individual animal feeding and observation data were not submitted; 5) the study reported that tetrachloroethylene, an antihelmenthic, was used several times a day. This chemical can cause effects on certain blood parameters. Since hematological effects were noted in the study, the possibility that this antihelmenthic chemical caused or contributed to these effects cannot be ruled out.; 6) limited clinical chemistries determinations; and 7) urinalysis determinations were carried out on cage collected urine. Based on the many deficiencies and reporting omissions in this study, which have not been satisfactorily addressed by the sponsor, the study can no longer be classified as core supplementary and has been down-graded to invalid.

- 1) 2-Year Feeding/Oncogenicity - rat: Principal study -- see previous description; core grade minimum (Ciba-Geigy Corp., 1986).
- 2) 1-Year Feeding - dog: Co-principal study -- see previous description; core grade minimum (Ciba-Geigy Corp., 1987a).
- 3) 2-Generation Reproduction - rat: See previous description; core grade minimum (Ciba-Geigy Corp., Agricultural Div., 1987b).
- 4) Developmental toxicity - rat: Core grade minimum (Ciba-Geigy Corp., 1984a).

Groups of pregnant Charles River rats (27/dose) were administered atrazine by gastric intubation at dose levels of 0, 10, 70 and 700 mg/kg-day. Dosing occurred daily and was performed on days 6 through 15 of presumed gestation. The control group received 10 ml/kg-day of 3% corn starch containing 0.5% Tween 80, which was the volume equivalent to that received by treated rats.

Maternal toxicity was observed during and after the treatment period at the 700 mg/kg-day dose level (HDT). Signs of toxicity in the HDT included death (21 of 27 dams), reduced food consumption, reduced weight gain, salivation, ptosis, swollen abdomen, oral/nasal discharge and bloody vulva. Maternal toxicity was also observed at the 70 mg/kg-day dose level. Toxicity signs in this group included reduced food consumption, reduced body weight and reduced weight gain. No maternal toxicity was observed in the 10 mg/kg-day or control groups. Based on the above effects, the NOEL and LEL for maternal toxicity are 10 and 70 mg/kg-day, respectively.

At 70 mg/kg-day, there were statistically significant increases by both fetal and litter incidence in skeletal variations indicating delayed ossification. These included: skull not completely ossified, presphenoid not ossified, teeth not ossified, metacarpals not ossified, metacarpals bipartite, and distal phalanx not ossified. The incidences of these effects in the control and low-dose groups were comparable. Based on these effects, the NOEL and LEL for developmental toxicity are 10 and 70 mg/kg-day.

- 5) Developmental toxicity - rabbit: Core grade minimum (Ciba-Geigy Corp., 1984b)

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Groups of pregnant New Zealand White rabbits (19/dose) were administered atrazine at dose levels of 0, 1, 5 and 75 mg/kg-day on days 7 through 19 of gestation. The control group (vehicle control) received 5 ml/kg-day of 3% corn starch with Tween 80, which was a volume equivalent to that received by rabbits treated with atrazine.

Maternal toxicity was noted in the high-dose group only. From the body weight gain data, it is not apparent that there was a dose related decrease in body weight gain at all dose levels as originally reported. A treatment-related effect was noted in the body weight gain in the high-dose group during the dosing period, with a rebound increase in body weight gain following the dosing period. Combined-dosing period and post-dosing period body weight gain for the high-dose group also shows a decrease, as does the corrected body weight gain for the high-dose group. Food consumption data for these periods also support the observation of a high-dose group effect. Low food efficiency was noted in the high-dose group during the dosing period and for the combined period including the dosing period and post-dosing period. There appears to be increased food efficiency in the post-dosing period, which supports what was noted for food consumption and the rebound in body weight gain in the post dosing period. Other signs of maternal toxicity related to clinical observations included an increase in "stool: little, none and/or soft" in the high-dose group, along with the evidence of "blood on vulva/in cage" in the high-dose group. No treatment-related signs were noted in the low- or mid-dose groups. Cesarean section data showed no additional maternal toxicity data; however, developmental toxicity was noted at the high-dose in the form of increased total resorptions and resorptions per dam, decreased total live fetuses and live fetuses per dam (litter size), an increased post-implantation loss and a decrease in mean fetal weight. Therefore, based on the effects observed at the highest dose tested, the LEL for maternal and developmental toxicity is 75 mg/kg-day. The NOEL for maternal and developmental toxicity is 5 mg/kg-day.

Other Data Reviewed:

1) 91-Week Feeding/Oncogenicity - mouse: Core grade guideline (Ciba-Geigy Corp., Agricultural Division, 1987c).

Groups of CD-1 mice (60/sex/dose) were administered atrazine for 91 weeks at dietary levels of 0, 10, 300, 1500, and 3000 ppm (Male: 0, 1.4, 38.4, 194.0 and 385.7 mg/kg-day; Female: 0, 1.6, 47.9, 246.9 and 482.7 mg/kg-day). Animals received food and water ad libitum.

Dose-related reductions were observed in mean body weight gain in both sexes of mice receiving 1500 or 3000 ppm. In mice receiving 1500 ppm, the decrease in mean body weight gain at weeks 12 and 91 were 33% and 23% for males, respectively, and 14.3% and 11% for females, respectively. In mice receiving 3000 ppm, the decrease in mean body weight gain at weeks 12 and 91 were 40.6% and 24.4% for males, respectively, and 12.1% and 48.5% for females, respectively.

At the termination of the study, statistically significant ( $p < 0.05$ ) reductions in mean erythroid variables (erythrocyte count, hematocrit and hemoglobin) were observed in mid- and high-dose males and high-dose females. High-dose females also had increased neutrophil percentage ( $p < 0.05$ ) and decreased lymphocyte

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percentage ( $p < 0.05$ ) when compared with controls.

Dose-related cardiac thrombi (primarily in the atria) were seen in male and female mice. The incidence for males was 3/59, 6/60, 3/60, 7/60 and 9/58 for the 0, 10, 300, 1500 and 3000 ppm dose groups, respectively. The incidence for females was 3/60, 4/59, 2/60, 11/60 and 26/60 for the 0, 10, 300, 1500 and 3000 ppm dose groups, respectively. This effect was observed primarily in those animals who had died or were killed in the course of the study.

Based on the above effects, the LEL for systemic toxicity is 1500 ppm (Male: 194.0 mg/kg-day; Female: 246.9 mg/kg-day). The NOEL for systemic toxicity is 300 ppm (Male: 38.4 mg/kg-day; Female: 47.9 mg/kg-day).

2) Developmental toxicity - rat: Core grade minimum (Ciba-Geigy, Corp., 1971).

Groups of pregnant rats were administered atrazine by gavage at dose levels of 0, 100, 500 and 1000 mg/kg-day on days 6 through 15 of gestation. In the high-dose group, 7 out of the 30 animals treated died. Slight weight losses in females were observed at mid-dose. A reduction in mean fetal weights and an increase in the number of embryonic and fetal resorptions were observed in the mid- and high-dose groups. Based on the above effects, the NOEL and LEL for maternal toxicity and fetotoxicity are 100 and 500 mg/kg-day, respectively.

Data Gap(s): None

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CONFIDENCE IN THE RfD

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Study: High

Data Base: High

RfD: High

The principal studies are of good quality and are given high confidence ratings. Additional studies are supportive of the principal studies and of good quality. Therefore, the data base is given a high confidence rating. High confidence in the RfD follows.

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EPA DOCUMENTATION AND REVIEW

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Source Document: This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation: None

Agency Work Group Review: 07/08/86, 12/09/86, 05/20/87, 06/22/88, 02/21/90, 11/04/92, 12/16/92, 09/23/93

Verification Date: 09/23/93

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EPA CONTACTS

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## REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

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- Healy, M.R.C. 1972. Animal Litters as Experimental Units. J. Royal Stat. Soc. (Series C), Applied Statistics. 21(2): 155-159.

## REVISION HISTORY

03/88 RfD Confid: Confidence levels revised  
08/88 RfD Data: Withdrawn; new oral RfD in preparation  
09/88 RfD Data: Revised oral RfD summary added  
03/90 RfD Data: Withdrawn; new oral RfD in preparation  
03/90 RfD Refs: Oral RfD references withdrawn  
05/90 RfD Data: Oral RfD summary replaced; RfD unchanged  
05/90 RfD Refs: Oral RfD references replaced  
01/91 RfD Data: Text edited  
12/92 RfD Data: Oral RfD summary noted as pending change; review date ad  
01/93 RfD Data: Withdrawn; new oral RfD in preparation  
10/93 RfD Data: Oral RfD summary replaced; RfD changed

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